[*Reprinted from the Journal of Physiology.*
Vol. XXVI. No. 1, 1900.]

ON THE CHANGES IN VOLUME OF THE SUBMAXILLARY GLAND DURING ACTIVITY.

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Changes in volume of the submaxillary gland may be brought about both by variations in the flow of blood to the gland and of secretion from the gland.

The circulation in the vessels of the submaxillary gland has been already investigated by more than one observer, but the methods employed up to the present have varied but little. It has been customary either to collect the blood escaping directly from one of the gland veins or from the lower division of the jugular vein after tying all the branches opening into it except the veins from the submaxillary gland. Inasmuch as these methods involve bleeding of the animal which is under observation and therefore directly affect the irritability both of vaso-motor and secretory fibres, and probably also of the gland-cells, it is only in the earlier stages of the experiment that reliance can be placed upon the results thus obtained. I have therefore been led to contrast these results with those obtained by a method which records graphically the vaso-motor changes of the gland vessels and the changes which occur in the volume of the gland during activity, but does not involve any bleeding of the animal during the course of the experiment.

[1] Towards the expenses of this research a grant was made by the Royal Society.

My thanks are due to Prof. Schäfer for suggesting the research, to Prof. Starling for much valuable assistance during its progress, and to Prof. Langley for some kindly criticism and suggestions.

Method.

Changes in volume of the submaxillary gland were recorded by means of a plethysmograph of very simple construction, devised by Prof. Schäfer, which consists of a gutta-percha box with one side of glass, thus enabling the gland to be kept directly under observation and any flushing or pallor of the superficial vessels to be accurately noted. The gland is exposed below the angle of the jaw, and stripped free from its capsule, and the duct is also cleared for a small portion of its length from any attachments of connective tissue, so that both the gland and part of the duct are freely moveable. Occasionally it is necessary to tie one or two small veins, if these are present on the side of the gland farthest away from the hilum, but care is taken to leave the largest veins, so that there may be no possibility of venous congestion. The vessels and gland-duct enter the box on one side through an opening sufficiently large to prevent any pressure being exercised on them, and the rest of the aperture is closed by cotton-wool and thick vaseline. Only a very small portion of the duct when it emerges from the hilum is contained within the plethysmograph, and the box is so supported by means of a clamp that the portion of duct outside it is quite loose and no contraction of the longitudinal fibres of the duct can pull upon or otherwise affect the volume of the contents of the box. The plethysmograph is well warmed before the gland is placed within it, and in addition some cotton-wool moistened with warm normal saline solution is used both to support the gland and to prevent its becoming dry or cool. The box is connected with a tambour or piston-recorder by an india-rubber tube attached to a glass tube which passes through one side of the box, the whole apparatus being filled with air. A lateral tube leads from this connecting tube, and is closed with a spring clip, so that the pressure within this air-tight system can be raised or lowered at any moment. The piston-recorder is made to write on smoked paper on a revolving drum, and the tracings obtained in many cases show most distinctly both heart-beats and respiratory curves. In every case dogs were employed, and the anæsthetic was varied in different experiments, so that any influence due to this cause alone might be discounted by comparative observations.

Nicotine.

Intravenous injection of small doses of nicotine causes a diminution in the gland-volume lasting from 1 to 2 minutes and accompanied by a rise of general blood-pressure (Fig. 1) and an initial flow of secretion from the duct.

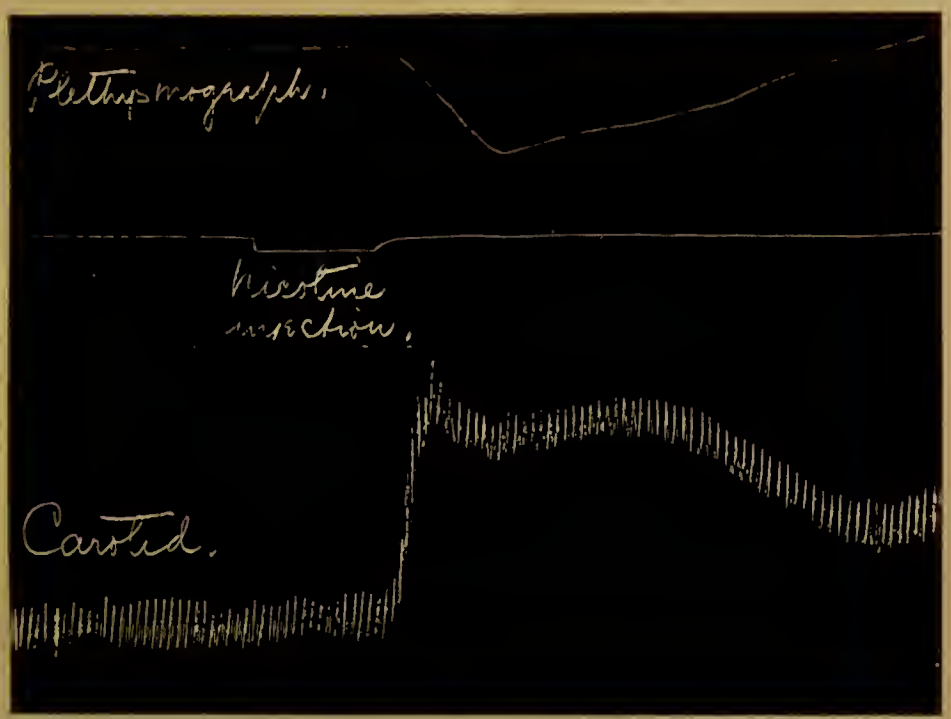

Fig. 1. Dog. 9·6 kilos. Effect on gland-volume and on blood-pressure of intravenous injection of 2 mg. nicotine.

If similar small doses be repeated at short intervals, in each case before the effect of the preceding dose has passed off, the additional effect on the gland-volume produced by each injection becomes less and less, until the gland attains its maximal capability of reaction to the nicotine stimulus. If, however, the at first small doses of nicotine be progressively increased, the maximal shrinkage of the gland in response to nicotine is attained with a smaller total amount of the drug injected if the intervals between the successive injections be kept the same, and the gland may be retained thus under the maximal influence of nicotine and the flow of secretion kept continuous by injecting slightly increasing doses at increasingly longer intervals. With reference to such an effect on the secretion of the gland, the suggestion has been made by Langley[1] that with successive doses the paralysing effect

[1] This *Journal*, XI. p. 148. 1890.

of nicotine upon the nerve cells decreases more than the stimulating effect.

The effect of nicotine upon the vaso-motors of the submaxillary gland can be investigated plethysmographically by giving such a dose of atropine as will produce paralysis of the secretory fibres of the chorda (10 mg. for a dog weighing 7 kilos.) and then injecting a small dose of nicotine into a vein. This gives rise to a diminution in the volume of the gland, but also to some amount of secretion from the duct. This is no doubt due to the fact that atropine does not paralyse the secretory fibres of the sympathetic, and the injection of nicotine stimulates the cells with which they are connected to secretion. If now when the secretion has ceased the gland-duct be clamped, and a further small dose of nicotine injected, there is still produced a preliminary shrinkage of the gland followed by dilatation. This diminution in gland-volume is due to the vaso-constrictor action of the drug, and the succeeding dilatation of the gland is due either to mere passive distension as a result of the blocking of the duct, or partly to an associated dilatation of the gland vessels.

That nicotine has a peripheral action on the vessels of the submaxillary gland appears probable from the results obtained by repeating the former experiment after the chorda has been divided and the superior cervical ganglion excised. Vaso-constriction was again produced by nicotine injection, followed as before by swelling of the gland.

Coniine has an action similar to nicotine on the vessels of the gland, but its action is less powerful and a larger dose must be given in order to produce the same effect.

When employing a solution of nicotine freshly prepared by Martindale I have found that uniformly smaller doses of the drug were required to produce temporary paralysis of nerve cells, whether of the chorda or sympathetic, than those described by Langley[1]. In a dog weighing 7·2 kilos, after intravenous injection of 1.0 mg. of nicotine stimulation of the chorda produced dilatation of the gland, but no flow of secretion from the duct for a period of 10 minutes. In a dog of about the same weight a dose of 17 mg. of nicotine abolished all effect of chorda excitation on the gland for a similar length of time, while in another dog paralysis of the sympathetic for a space of 10 minutes was brought about by a dose of 40 mg. Very considerably larger doses are necessary if, instead of one big dose several smaller doses of the drug

[1] It is possible that this may be due to an increased vulnerability of the gland cells due either to exposure of the gland or to a certain amount of anæmia of the cells.

are injected, and under such circumstances it appears that the total amount of nicotine necessary to produce paralysis depends largely upon the length of time allowed to elapse between the first injection and the final effective dose, a larger amount being required the longer the interval allowed.

In these experiments on the action of nicotine, in order to avoid the respiratory paralysis produced by the intravenous injection of nicotine and coniine, the animal was placed under artificial respiration, and either both vagi were divided in the neck or sufficient atropine was given to eliminate the action of the vagus on the heart.

Pilocarpine.

Intravenous injection of small doses of pilocarpine (1 mg. in a dog weighing 7·6 kilos) causes a primary slight dilatation of the gland followed by diminution of its volume owing to the free flow of saliva from the duct. The primary swelling of the gland when present, is brought about by the free flow of blood which the administration of pilocarpine induces, but in spite of continued vaso-dilatation the gland speedily begins to diminish in total bulk, and remains thus as long as the drug continues to cause increased secretion, after which it gradually returns to normal. If a second dose of pilocarpine be injected, or the chorda stimulated before the first dose has ceased to act, the gland-volume undergoes still further diminution, proportional to the strength and duration of the stimulus, or to the dose of the drug. When, however, a maximal secretion has been induced by the first injection of pilocarpine, neither further injections of the same substance nor chorda stimulation produce any effect on the gland volume. It has been shown by Langley that pilocarpine still causes its effect after the chorda has been divided and the superior cervical ganglion excised. I have, however, failed to obtain the primary vaso-dilator effect on pilocarpine injection after division of the chorda, though the secondary shrinking of the gland was but little affected (Fig. 2); it seems, therefore, that the peripheral secretory fibres of the chorda are more readily acted upon by pilocarpine than the dilator.

If, after the administration of small doses of pilocarpine intravenously, the sympathetic be stimulated, there occurs at first an augmentation of the gland shrinkage due to a preliminary increased flow of saliva, which is maintained, and sometimes exceeded by the subsequent

diminution in gland-volume due to vaso-constriction, even though the secretory flow diminishes as a result of the nerve excitation.

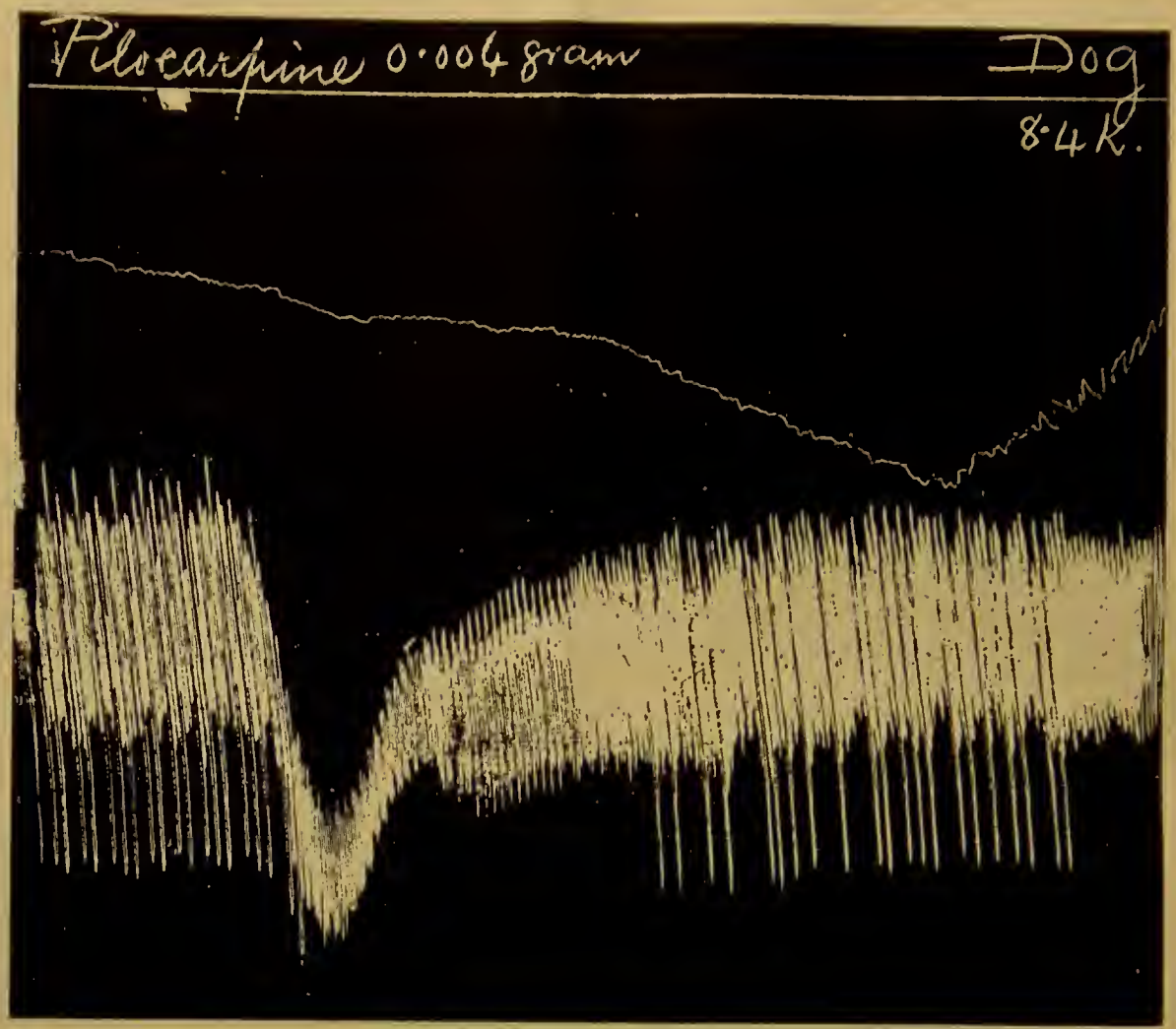

Fig. 2. Dog. 8·4 kilos. Effect on volume of submaxillary gland and on blood-pressure of intravenous injection of 4 mgs. of pilocarpine after division of chorda. Anæsthetic A.C.E. Amount of secretion from gland 0·8 c.c.

Intravenous injection of extract of mammalian suprarenal causes vaso-constriction and diminution in volume of the gland (Fig. 3). Injection of brain extract (decoction of fresh brain in dose of 2·2 c.c. for dog of 6·8 kilos) produces a fall of general blood-pressure and slight diminution in gland-volume followed by dilation of the gland, which is not prevented by the previous administration of atropine[1] (Fig. 4).

If the submaxillary gland be excised on one side, and a saline decoction made from it and injected intravenously into the same dog, the effect on the remaining submaxillary gland of the opposite side is to produce a preliminary diminution, followed by a slight increase in

[1] Cf. Osborne and Vincent, This *Journal*, xxv. p. 283. 1900.

volume, accompanied by a fall of general blood-pressure, but no definite effect upon secretion (Fig. 5).

Fig. 3.

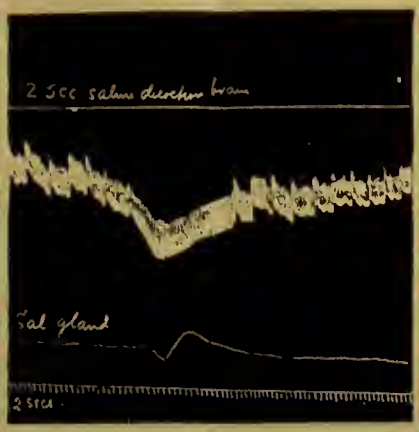

Fig. 4.

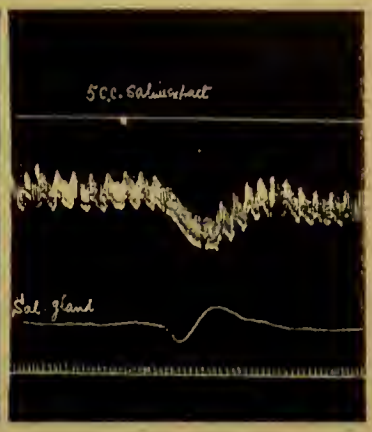

Fig. 5.

Fig. 3. Dog. 8·5 kilos. Effect on volume of submaxillary gland and on blood-pressure of intravenous injection of suprarenal extract equal to 20 mgs. of fresh gland.

Fig. 4. Dog. 7·8 kilos. Effect on submaxillary gland-volume and on blood-pressure of injecting intravenously a saline decoction equivalent to 0·5 grms. of brain extract. Time marker = 2 secs.

Fig. 5. Dog. 10·4 kilos. Effect of intravenous injection of saline extract representing 1·2 grms. of submaxillary gland removed from opposite side of neck of same animal. Time marker = 2 secs.

Curare has been shown to diminish the conductivity of the vaso-dilator fibres of the chorda, and hence it might be expected that in a curarised animal the diminution in volume of the gland, which is described later in this paper as being brought about by chorda stimulation, would be greater for the same strength and duration of stimulus than in the same animal before the administration of curare. This is, however, not found to be the case, either because curare also directly affects the secretory fibres of the chorda or the gland cells, or because the cells secrete less, owing to the somewhat diminished flow of blood to the gland brought about by chorda excitation after curare has been given.

Asphyxia.

In these experiments the dog was under the influence of curare. During the early stages of asphyxia the volume of the gland underwent diminution, but later on when the general blood-pressure was considerably raised the gland dilated. That this dilatation is passive is shown by employing a mercury-valve.

In some experiments, towards the later stages of asphyxia, the

gland diminished slowly in volume, and this diminution was accompanied by a flow of secretion from the duct when the chorda was intact, but this result was not obtained in one experiment after both chorda and superior cervical ganglion on the same side as the gland under observation had been divided.

Vagus.

Changes following stimulation of the peripheral cut end of the vagus are purely passive. Such stimulation brings about an almost immediate diminution in volume of the gland, which persists as long as the heart is stopped. As soon as the current is shut off the gland immediately tends to resume its original bulk, and, if the stimulus has been of moderate strength, the plethysmographic lever then rises to a level still higher than that at which it stood before the excitation. This after-dilatation persists for a short time, and the lever then gradually falls again to normal. Fig. 6 shows this after-effect, but,

Fig. 6.

Fig. 7.

Fig. 6. Dog. Stimulation of peripheral end of cut vagus causes diminution in gland-volume succeeded by dilatation. This secondary dilatation is not accompanied by any corresponding variation in the general blood-pressure curve. Anæsthetic: Ether, curare.

Fig. 7. Dog. Effect of stimulation of central end of divided vagus on side opposite to that of gland, vagus on same side being also divided.

inasmuch as the general blood-pressure is not raised as a result of the vagus stimulation, it must be held that the after-dilatation is

due to relaxation of the vessels of the gland following temporary ischæmia.

Stimulation of the central end of the divided vago-sympathetic in a curarised dog on the side opposite to that of the gland under observation, the other vagus also being cut, causes at first a slight passive dilatation of the gland accompanying the general rise of blood-pressure, but after a considerable latent period this is succeeded by a diminution in gland-volume and a slow flow of somewhat viscid secretion (Fig. 7). When the central end of the vagus on the same side as the gland is stimulated, the passive dilatation due to reflex rise of blood-pressure is outbalanced by the direct effect of the sympathetic on the vessels and secreting cells.

Sympathetic.

The constriction of the vessels of the submaxillary gland caused by sympathetic stimulation, even if the stimulus be weak and applied

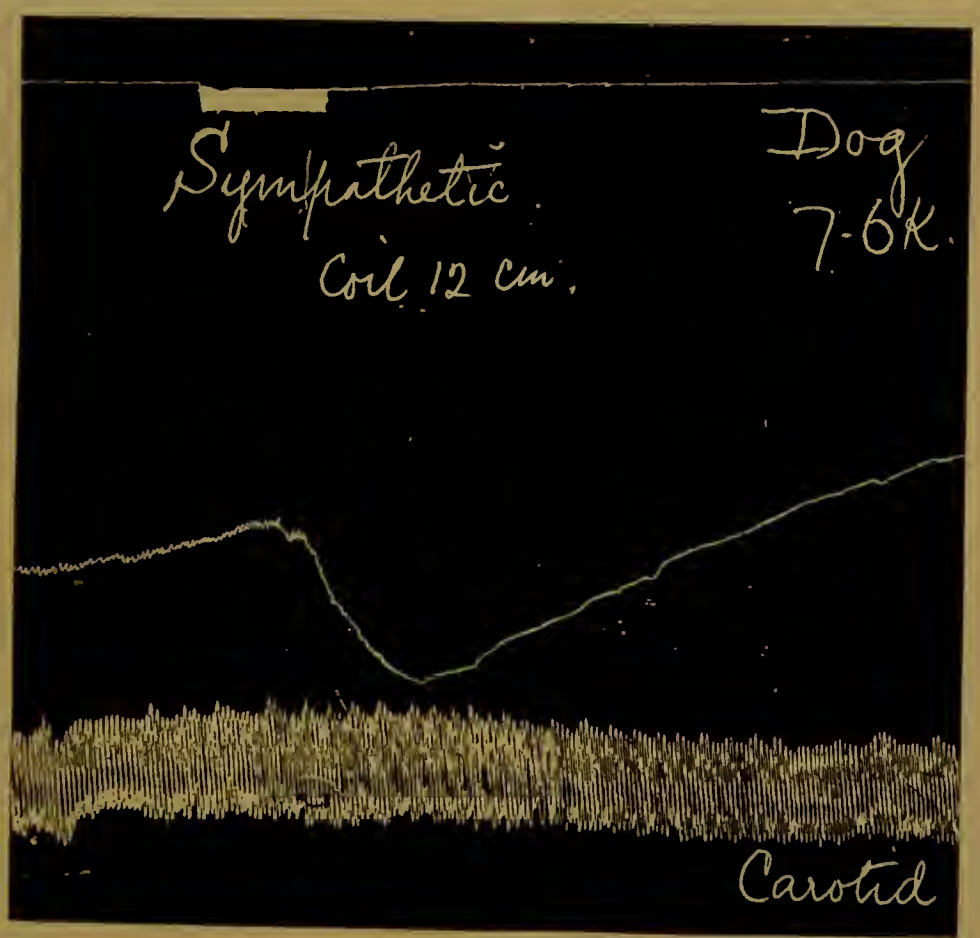

Fig. 8. Dog. Effect on gland-volume of excitation of peripheral end of divided cervical sympathetic. After-dilatation of gland is seen. Heart-beats are distinguishable on plethysmographic tracing.

only for a short time, is sufficient to cause considerable diminution in volume of the gland and fall of the piston-recorder lever, apart from the effect which is brought about by the secretory fibres when the nerve is stimulated (Fig. 8). The surface of the gland stripped of its capsule can be seen to become pale. The sympathetic effect is preceded by a short latent period (1—2 secs.), and is followed by an after-effect when the current has been shut off; the duration of both is, however, shorter than when the chorda is stimulated.

Prolonged stimulation of the sympathetic with a moderate or strong current produces an effect on the gland-volume which is only slowly recovered from (Fig. 9). If immediately after such sympathetic

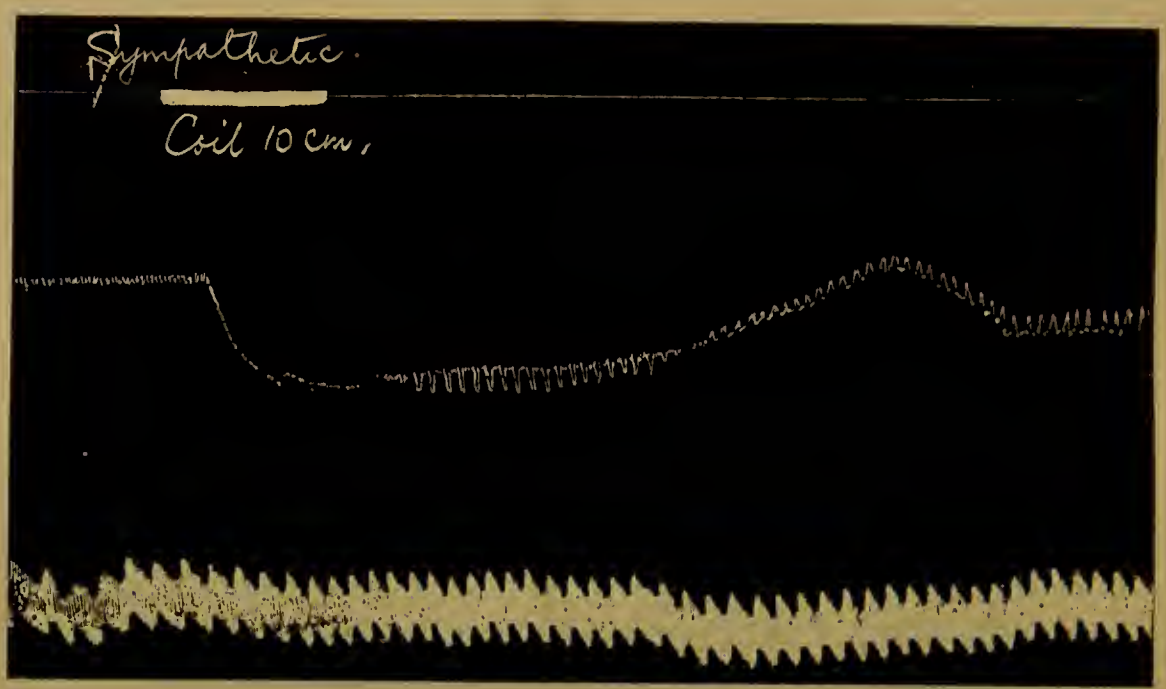

Fig. 9. Dog. Effect of somewhat more prolonged stimulation of divided sympathetic. Heart-beats and respiratory waves are seen on tracing.

stimulation the chorda be stimulated, the fall of the plethysmographic lever is usually replaced by a rise (Fig. 10), sometimes of considerable extent if the sympathetic secretion is very viscid.

If the sympathetic stimulation has been prolonged, this rise of the plethysmographic lever may persist for some time, but it is finally changed again to a fall as the normal chorda effect returns.

The maximum amount of diminution of gland-volume is obtained by stimulating the sympathetic strongly after repeated chorda excitations. The fall of the lever is then greater than I have succeeded in obtaining by any other method of submaxillary nerve excitation, and it does not immediately pass off when the current is stopped.

Chorda.

The chorda was exposed after division of the digastric muscle on the same side as the submaxillary gland under observation, ligatured

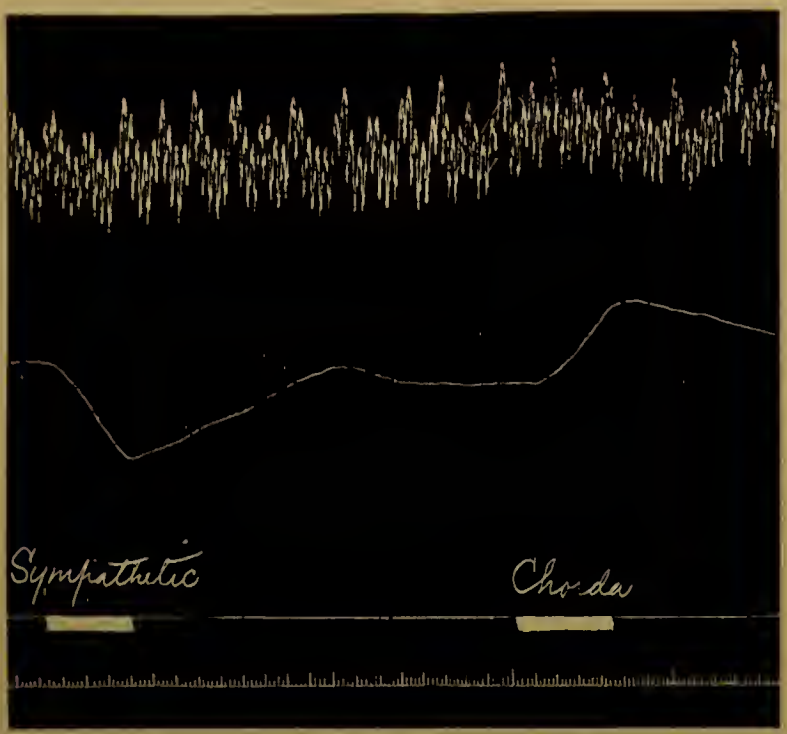

Fig. 10. Dog. Effect on gland-volume of stimulation, first of sympathetic, and then of chorda tympani.

and cut, and the peripheral end stimulated by means of Ludwig's electrodes which were left *in situ*. In some cases the chorda-lingual nerve was divided centrally, and the peripheral end stimulated; any injury to the more slender chorda nerve through manipulation was thus avoided. The nerve was excited by currents of different strengths, and with varying rates of repetition of the stimulus, and the anæsthetic was varied in different experiments. With a stimulus so weak that it was barely perceptible to the tongue, excitation of the chorda produced considerable diminution in volume of the gland and a fall of the lever of the piston-recorder. The fall was preceded by a short latent period when the gland was secreting freely, and rapidly reached its maximum when the excitation was a short one. When the current was shut off the lever still remained at its lowest point for a short period, which varied according to the duration of the passage of the current, the gland then very gradually again increased in volume and the lever slowly rose until it once more reached the base line. This recovery in volume

was succeeded by dilatation of the gland, and a further rise of the lever to a point well above the base line, after which it again gradually fell (Fig. 11). The extent of this dilatation varied according to the previous diminution in volume of the gland, being greater and more prolonged when the diminution of the gland-volume had been well-marked, but the after-rise of the lever did not equal in extent or duration its previous fall.

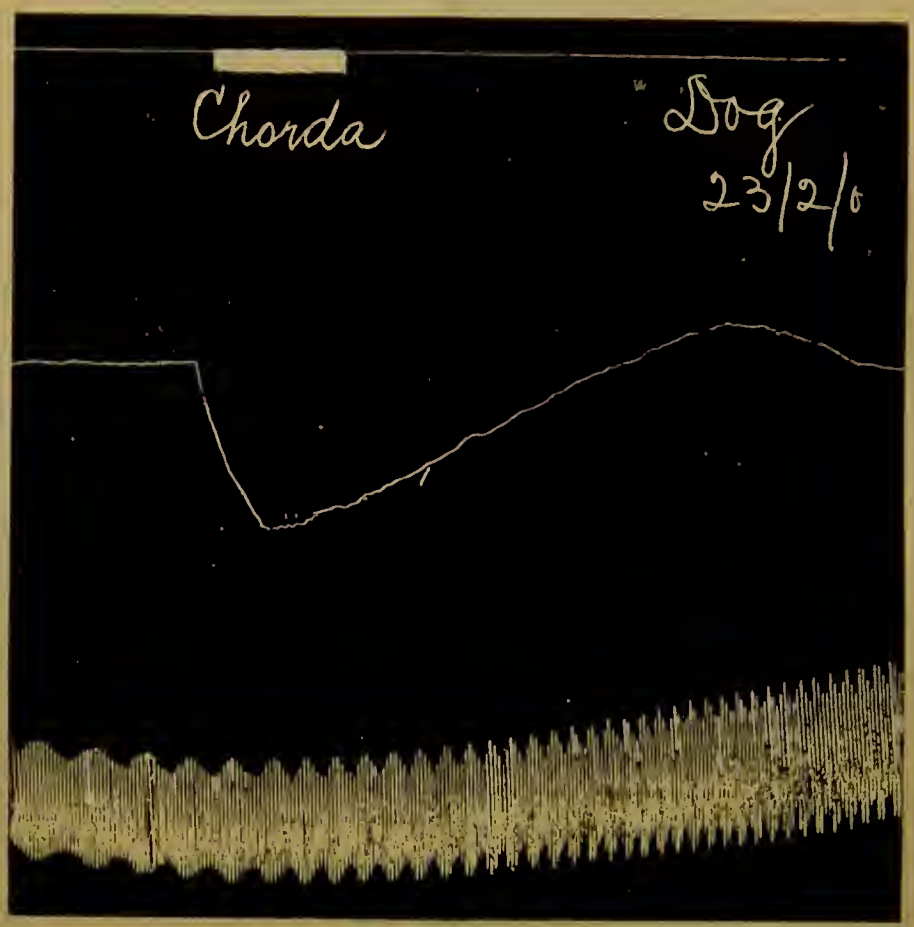

Fig. 11. Dog. Effect on volume of gland of stimulation of divided chorda tympani.

This diminution in gland-volume was accompanied by a free flow of secretion from the duct, the amount of which was measured, and by marked dilatation of the vessels of the gland, which rendered precautions necessary in order to ensure the free escape of blood through the gland veins.

With a stronger stimulus, the latent period was shorter, the flow of saliva greater, and the diminution in volume of the gland more abrupt and of greater range. The recovery of volume was also slower, and the after-dilatation more marked. When the excitation was a long one,

more especially with a strong current, the recovery of the gland was considerably prolonged and the rise of the lever a very gradual one. As long as both gland and nerve remained in good condition, and had not diminished in irritability either from cooling or drying, successive stimulations of the chorda repeated as soon as the gland had returned to its original volume still continued to produce the same effect, with but little difference in diminution of volume in response to stimuli of the same strength and duration. If, however, the nerve was stimulated a second time, either immediately after the first excitation, or while the lever was still rising, the resulting diminution in volume of the gland was less than that preceding it, this difference being greater the more quickly the second excitation succeeded the first.

When the secretion produced by chorda stimulation was scanty and viscid, in spite of the accompanying active vaso-dilatation, stimulation of the nerve caused either a very small fall of the lever, or a preliminary fall succeeded by a rise. In some cases, more especially when there was some obstruction to the free escape of blood through the veins and also scanty secretion, chorda excitation gave rise to increase of volume of the

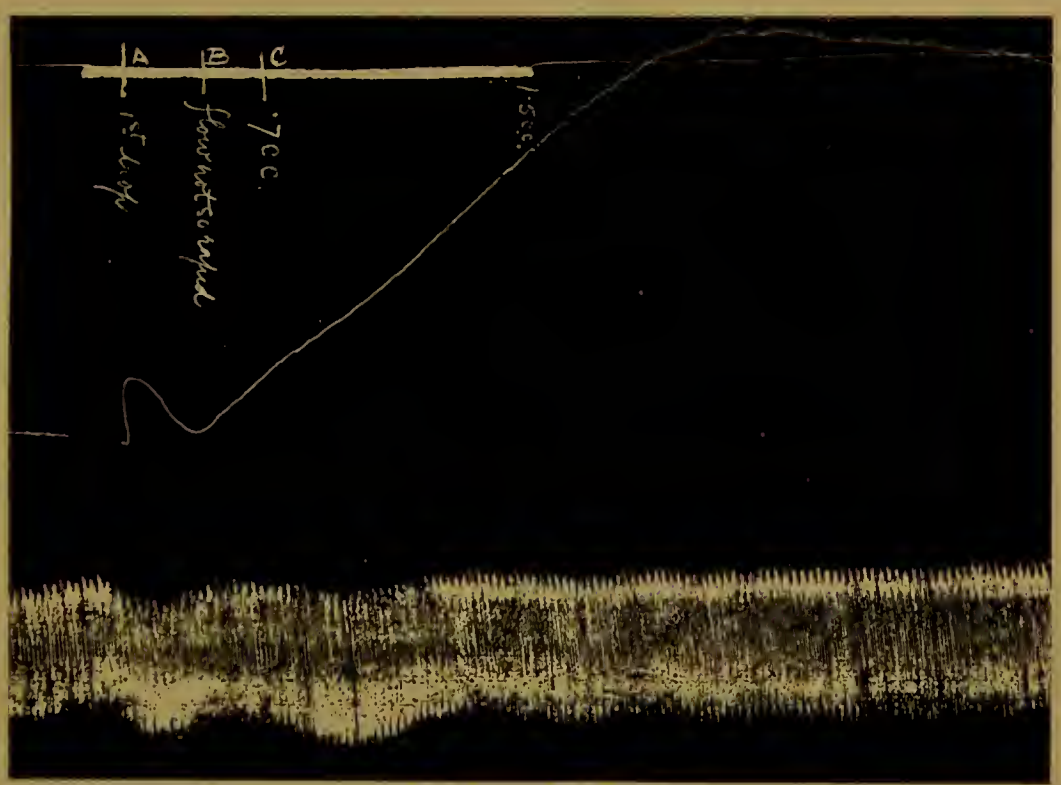

Fig. 12. Dog. 10·6 kilos. Stimulation of divided chorda with coil at 10 cm. for a period of 3 minutes. During this time 1·5 c.c. of fluid were secreted. After cessation of the stimulus the gland underwent further dilatation. At the point marked *A* the first drop of secretion escaped from the duct, at *B* the flow began to be less rapid, at *C* an amount equal to ·7 c.c. had been secreted.

gland, owing to the increased flow of blood to the gland more than compensating for the small amount of secretion leaving it. Fig. 12 is a record of the volume of the submaxillary gland where the chorda was stimulated continuously for a period of three minutes after all the veins leaving the gland had been ligatured with the exception of one small one. After a short latent period the gland dilated, but this dilatation was succeeded by a return to its original volume as soon as the first drop of fluid was secreted. For the short time during which secretion was fairly rapid no increase in gland-volume occurred, but as fluid began to be secreted less copiously the volume of the gland increased again rapidly while the excitation was continued. When the stimulus was shut off 1·5 c.c. had been secreted from the duct. After cessation of the stimulus, the gland still continued to dilate for a time, and only very slowly returned to its original volume.

Excitation of the chorda with weak and slowly repeated stimuli at the rate of 1 per second, or even less, sometimes when the gland was previously secreting freely, gave rise to but scanty increase in the secretion from the duct and to a rise of the plethysmographic lever,

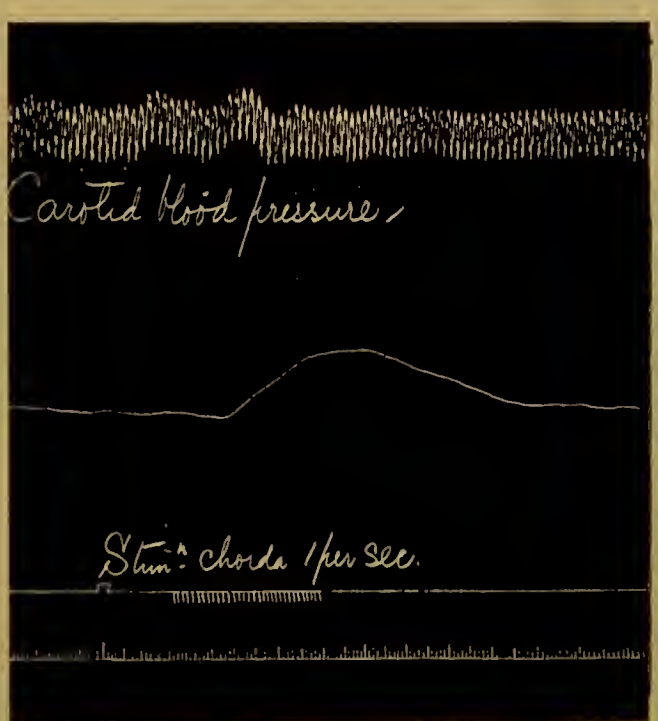

Fig. 13.

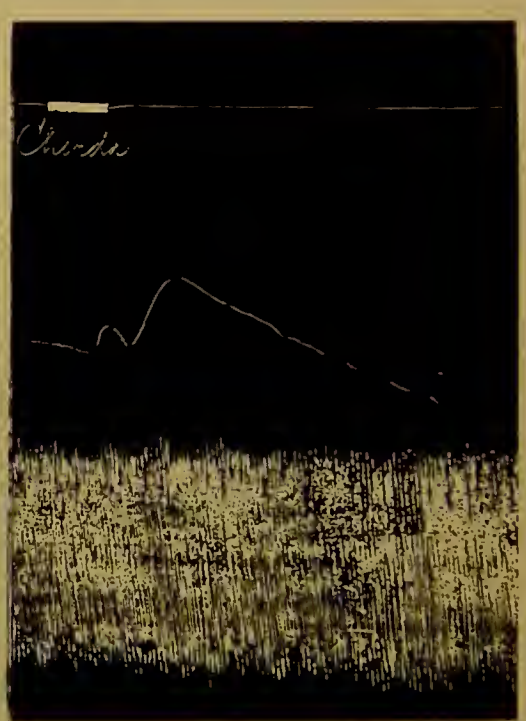

Fig. 15.

Fig. 13. Dog. Effect of repeated slow stimulation of chorda at rate of 1 per second. Coil at 12 cms.

Fig. 15. Dog. Effect on gland-volume of chorda stimulation. After a preliminary slight expansion of the gland a second more extensive dilatation occurred when the stimulus was removed.

due apparently to the vaso-dilator fibres of the chorda being more readily excited by such currents than the secretory (Fig. 13). If, however, such slow stimuli were continued for a considerable time the gland did in some cases finally diminish in volume, and a slow, slight secretion set in, the effect of which on the gland-volume outbalanced the vaso-motor effect, unless possibly the vaso-motor fibres are more readily fatigued by such stimuli than the secretory.

These results appeared to vary somewhat according to the anæsthetic used, and to be obtained more readily when the dog was under the influence of chloroform.

A triphasic effect was occasionally obtained on chorda stimulation, the gland-volume increasing very shortly after the current was sent into the nerve, and again diminishing to the normal after the current had been passing for about half a minute, when the flow of saliva had attained its first maximum, and then again increasing to the former level (Fig. 14) or beyond this (Fig. 15) after the current had been shut off. In these experiments the secretory response of the gland to chorda stimulation was not below normal, the total amount of saliva secreted

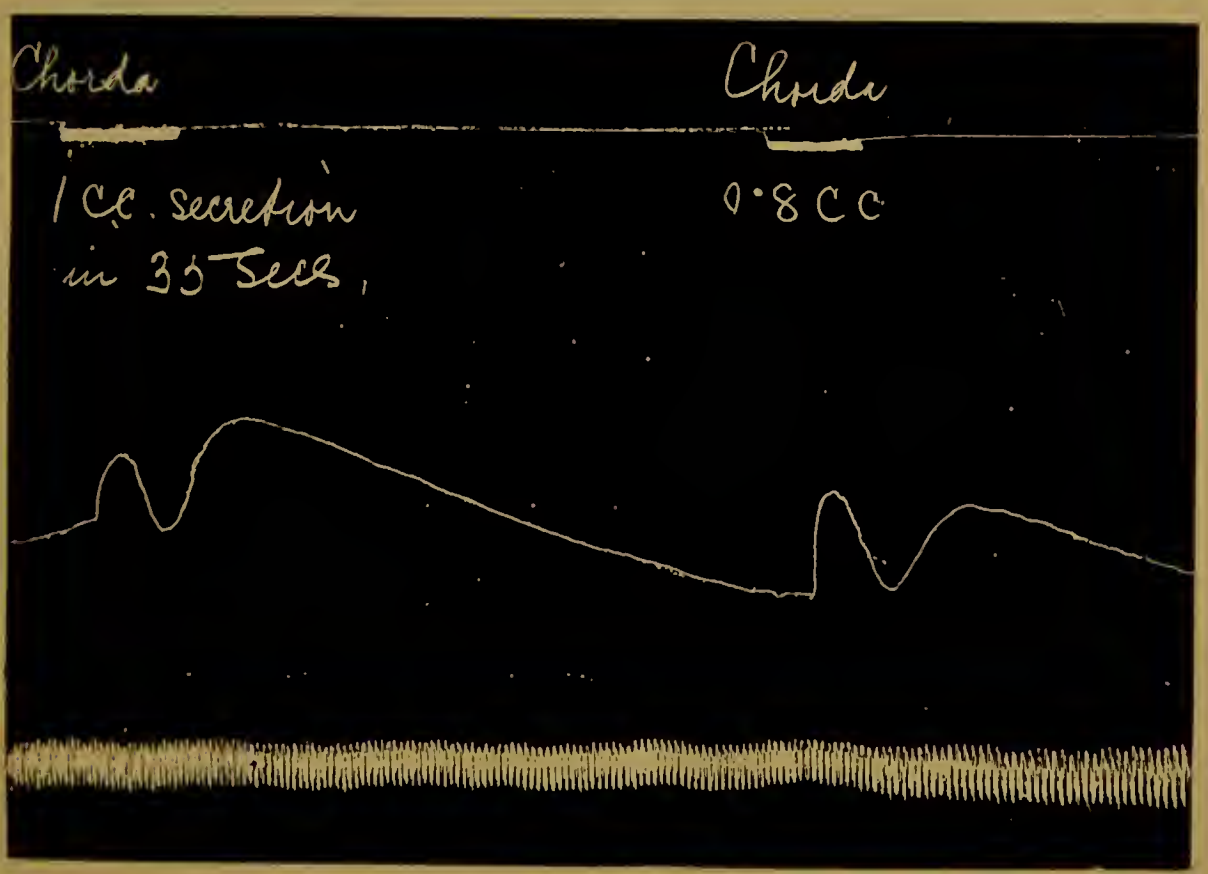

Fig. 14. Dog. Triphasic effect on volume of submaxillary gland of stimulation of chorda with weak current.

as a result of excitation of the nerve was not less than that obtained from other animals of similar size, and the nerve had not been exposed to injury or to excessive cooling. There was also no reason to think that the escape of blood from the gland was in any way interfered with. If it were not for the possibility of some slight unknown obstruction to the gland-duct leading to delay in the escape of saliva it would appear that, though the secretory fibres responded normally to stimulation, the vaso-motor fibres of the chorda were abnormally excitable, and this is borne out by the result of the subsequent administration of atropine in the same animal in sufficient doses to paralyse the secretory fibres, when stimulation of the chorda with weak currents gave rise to unusually extensive dilatation of the gland. This dilatation commenced at an interval after stimulation corresponding to the first rise on the tracings obtained before the administration of atropine, and lasted for an appreciable period after stimulation had ceased. When the tracing shown in Fig. 14 is compared with that obtained by mapping out the flow of saliva in a tube of fine bore at intervals of every five seconds (Fig. 16), it is seen that in this experiment the latent period of the

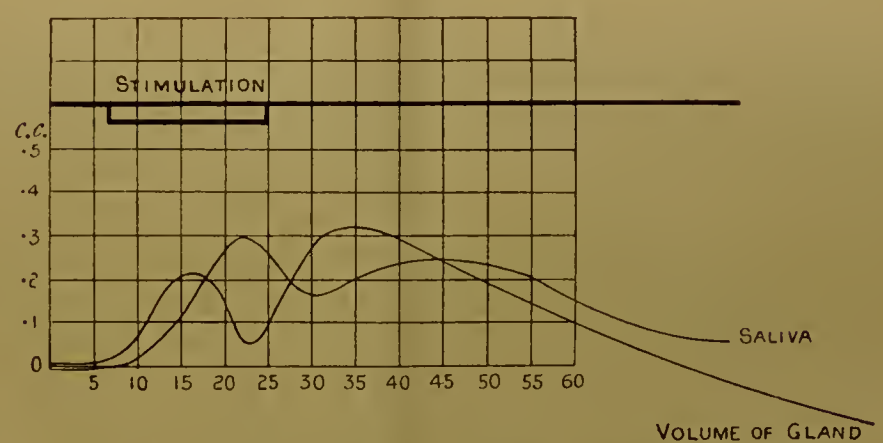

Fig. 16. Comparison of plethysmographic tracing seen in Fig. 14 with curve of saliva secreted from gland-duct during same period.

secretory fibres was longer than that of the vaso-motor fibres, and that as the flow of saliva attained its first maximum the previous expansion of the gland underwent diminution, the gland-volume again increasing as the flow of saliva once more diminished. In this experiment the second expansion of the gland was entirely an after-dilatation effect; the secretory effect, however, also underwent a temporary augmentation after the current had been shut off.

A triphasic effect as regards the secretion of the saliva was frequently obtained when the chorda was being stimulated for several

minutes. After a short latent period a flow of saliva commenced, which reached its maximum about the end of the first half minute, and then declined again, until at the end of the first minute or minute and a half the flow was only half as fast. The flow then became more rapid again, attaining its second maximum at the end of the first two and a half or three minutes, and then again diminishing during the remainder of the period of stimulation.

After the administration of small doses of atropine intravenously, sufficient in amount to paralyse the secretory fibres of the chorda (8—12 mg. for a dog of 7 kilos), stimulation of the peripheral cut end of the chorda caused no flow of secretion from the duct, but an active dilatation of the gland, and a rise of the piston-recorder lever to an extent about equal to the previous fall of the same lever brought about by a stimulus of the same strength and the same duration before any atropine had been administered. The dilatation was preceded by a short latent period, which was shorter according as the stimulus was

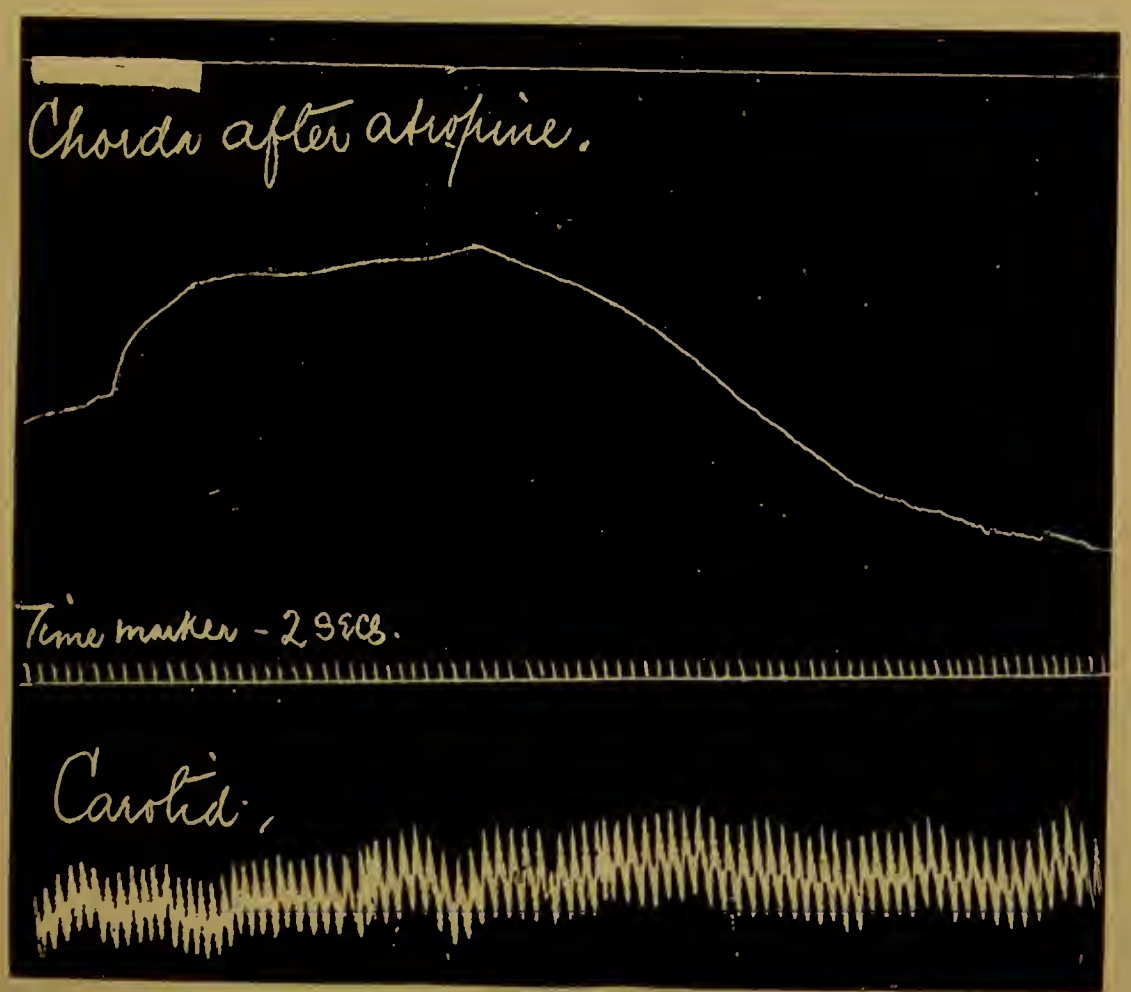

Fig. 17. Dog. 8·2 kilos. Effect of chorda stimulation after intravenous injection of 10 mgs. of atropine.

stronger, after which the recording lever rose somewhat rapidly and remained raised as long as the current was passing, and only gradually fell after the current had been shut off, the fall not always commencing until after an appreciable interval (Fig. 17). In one experiment where atropine was also given a large vein leaving the submaxillary gland was divided outside the plethysmograph and the flow of blood from it compared with the variations in volume of the gland produced by nerve stimulation. It was found that an increase took place in the gland-volume before any increase in the flow of blood from the vein on stimulation of the chorda, but that this interval became shorter as the strength of the current was increased. It seems probable that this result was due to the dilatation of the vessels of the gland produced by chorda stimulation necessitating an influx of additional blood to the gland in order to fill the vessels, so that in spite of the increased flow of blood due to the stimulation an interval necessarily elapsed before this increased flow made itself felt in the gland veins, and the amount of blood leaving the gland became greater than normal.

The absolute increase or diminution in volume of the gland under various conditions was estimated by calibration of the piston-recorder, the rise or fall of the lever for variations of fractional parts of a cubic centimetre being marked out on a scale. Inasmuch as the point of the lever necessarily moved through the arc of a circle, verticals were drawn either from the highest or lowest point of the curve, and calculations were based upon these measurements. The volume of the gland in cubic centimetres was determined from the difference between its weight in air and in water, and the amount of secretion produced by nerve stimulation or otherwise was also determined by connecting the cannula in the duct with a glass tube graduated in fractional parts of a c.c.

In order to calculate the total diminution in volume of the gland due to chorda excitation, the decrease in volume brought about by stimulation of the chorda was first determined in an etherised dog before any atropine had been given, and then the increase in volume of the same gland after the administration of a dose of atropine sufficient to paralyse the secretory fibres of the chorda. Thus, in one experiment the volume of the gland was 7·2 c.c., the diminution in volume of the same gland on chorda stimulation was 0·3 c.c., after atropine the expansion of the gland on excitation of the chorda was equivalent to 0·31 c.c. The total diminution in volume of the gland, and hence the maximum amount of secretion which could be eliminated from the cells

and alveoli of the gland as a result of this stimulation of the chorda amounted therefore to 0·3 + 0·31 c.c. = 0·61 c.c. The amount of secretion extended from the duct as a result of the nerve excitation amounted, however, to 0·71 c.c.; therefore 0·1 c.c. must have been derived either from the lymph spaces outside the gland or from the blood vessels. It has recently been shown by Bainbridge[1] that the flow of lymph from the submaxillary gland is not diminished, but rather increased during stimulation of the chorda, and that this increase of lymph flow may amount from 0·1 to 0·3 c.c. as a result of the nerve excitation. Almost all the secretion poured out by the gland when the secretory fibres of the chorda tympani are stimulated is, therefore, derived from the extra-vascular portions of the gland, and, although the fluid of the secretion must in the last instance be derived from the blood vessels of the gland, the influence of the secretory nerves appears to be almost exclusively on the secretory cells of the gland.

Effect of blockage of the duct on changes in the gland due to nerve stimulation.

When, previous to chorda stimulation, the duct is clamped or the cannula in the duct artificially blocked, excitation of the nerve produces a preliminary small fall of the tambour lever, followed immediately by a marked rise. If the duct be clamped during the time that the nerve is being stimulated and the gland secreting freely, this preliminary fall of the lever does not occur, but an immediate increase of the volume of the plethysmographic contents takes place. Removal of the clamp from the duct after the current has been shut off is followed by a fall of the lever (Fig. 18), and if then the chorda be again stimulated a still greater diminution in the gland-volume is produced. If, after the chorda has been stimulated for some minutes with the duct blocked, another 5—10 minutes be allowed to elapse before the clamp is removed, the secretory response of the gland to chorda stimulation is found to have become very imperfect. Excitation of the chorda after a small dose of atropine has been administered and the duct clamped produces an expansion of the gland considerably less than that obtained before administration of the atropine.

Continuous stimulation of the chorda with the duct blocked but no atropine administered causes an expansion of the gland greater than I

[1] This *Journal*, xxv. 1900 (*Proc. Physiol. Soc.* p. xvi.).

have obtained by any other means. A very considerable dilatation is obtained soon after the application of the stimulus, but the maximum increase in volume is only obtained after the current has been passing for some time, and is due to secondary changes taking place in the gland which cause it to become œdematous.

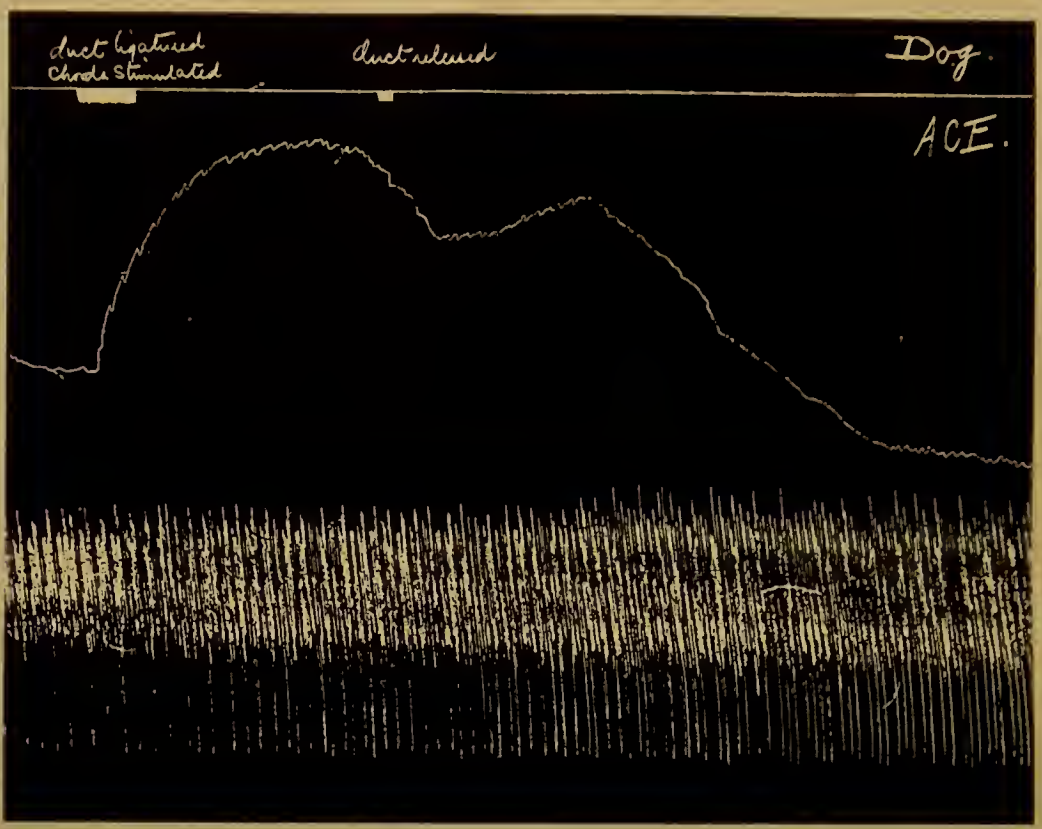

Fig. 18. Dog. 10 kilos. Effect on volume of gland of chorda stimulation after clamping of gland-duct. Previous to blockage of the duct the gland had been secreting well. Removal of the clamp was followed first by diminution of gland-volume, later by after-dilatation.

Effect on the volume of the submaxillary gland of variations in the amount of blood-flow.

It has been shown by Heidenhain that complete stoppage of the blood-flow to the submaxillary gland causes great diminution in the amount of saliva secreted during stimulation of the chorda. Complete cutting off of the blood-supply to the gland also causes a change in the response of the gland to chorda excitation, as estimated plethysmographically. If, however, the opposite carotid be ligatured and the carotid on the same side as the gland moderately compressed, a single chorda stimulation causes a diminution of gland-volume which differs but little from that obtained with the same strength of stimulus before

the carotids were obstructed. If the volume of the gland is allowed to return to normal before a second stimulus is applied, the response to chorda stimulation will again be good and the resulting flow of saliva from the duct abundant, and this result may be repeated with little variation for a period of at least 10 minutes from the first clamping of the artery if the gland is in good condition. The effective period of response to chorda stimulation after blocking of both carotids appears to be more prolonged if one or two superficial veins on the gland surface have previously been ligatured; it almost seems as if under such circumstances the gland has become accustomed to work under diminished blood-flow.

A certain amount of blood must reach the gland by way of the vertebrals and internal carotid, when there is no pressure in the external carotid, since the diminution in volume of the gland on chorda stimulation becomes less extensive on successive excitations if both subclavians be ligatured as well as both carotids, and a continued cessation of blood-flow to the gland finally brings about an absence of response to nerve stimulation. There may, however, be but little difference between the response to the first two excitations, if the second excitation occurs within 3 minutes of the first blocking of the vessels and after the lever has returned to the base line and the gland recovered from the effect of the first stimulus (Fig. 19).

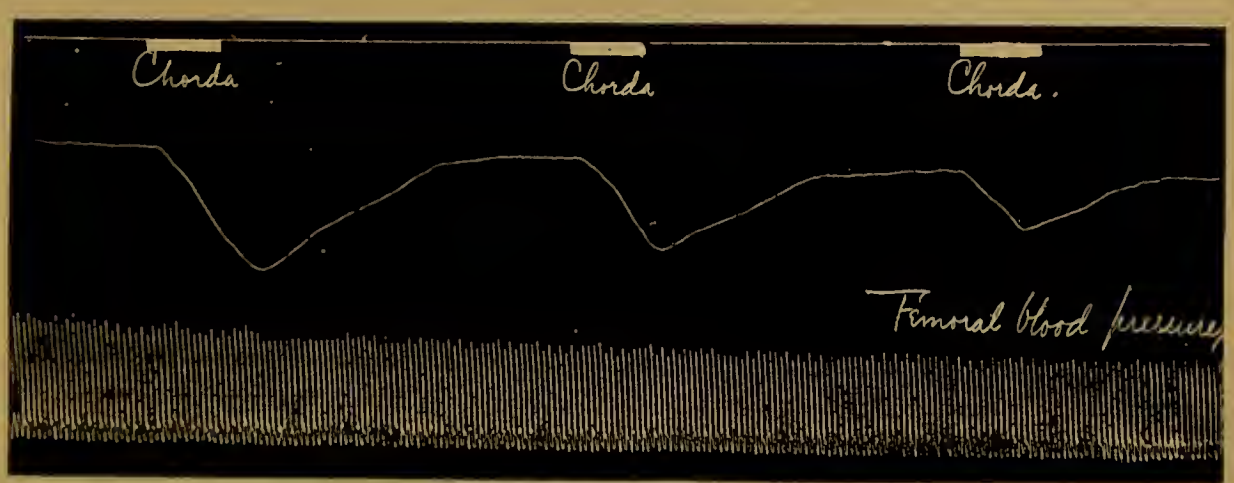

Fig. 19. Dog. Repeated successive stimulation of chorda with same strength of current after ligature of both subclavians. Blood-pressure tracing from femoral artery.

A peculiar result is sometimes obtained when, after blocking of the blood vessels the gland has ceased to respond effectively to nerve stimulation, the blood-flow is once more established and the chorda stimulated; instead of undergoing diminution in volume the gland

dilates somewhat (Fig. 20). This effect very soon passes off as the capability to secrete on chorda stimulation returns, and the usual

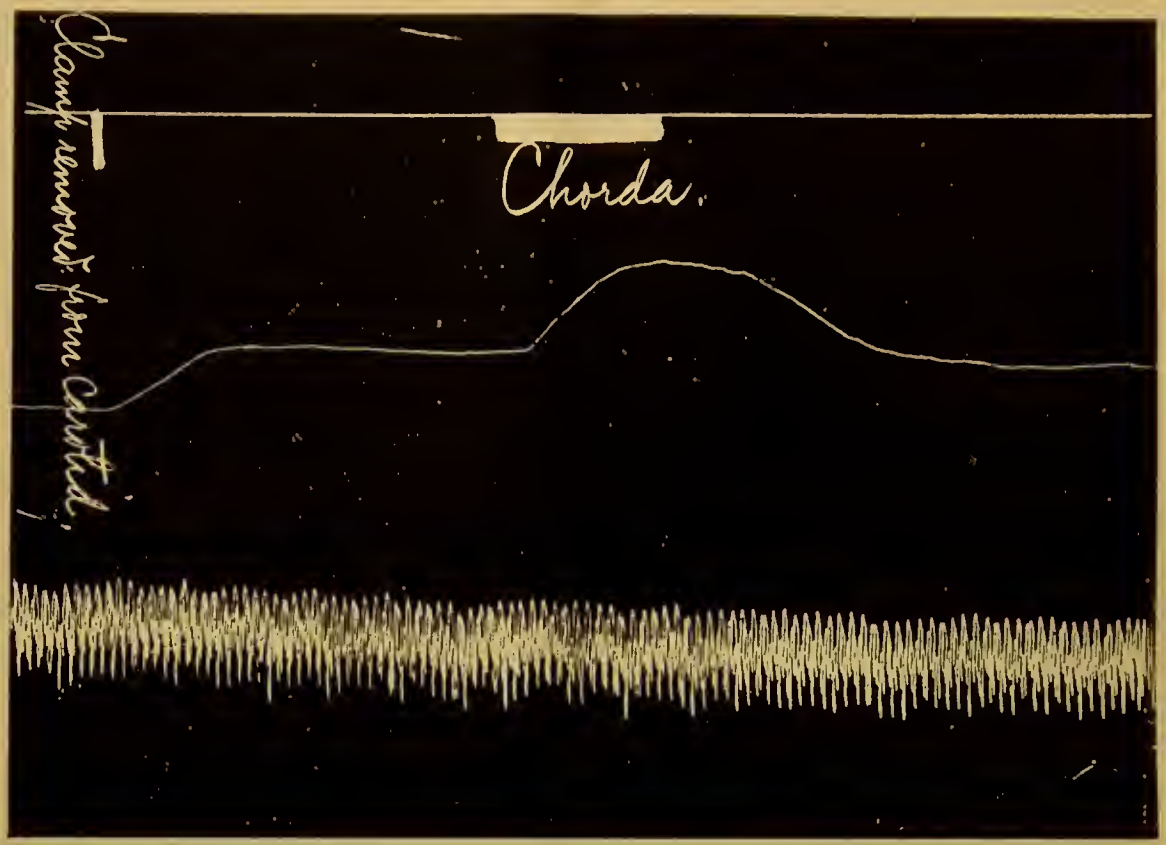

Fig. 20. Dog. The carotid on same side as gland was clamped for some time, the clamp was then removed and the chorda stimulated.

chorda effect takes its place. The explanation of this result is probably the fact observed by Heidenhain that after stoppage of the blood-flow to the gland the vasomotor fibres of the chorda recover more quickly than the secretory.

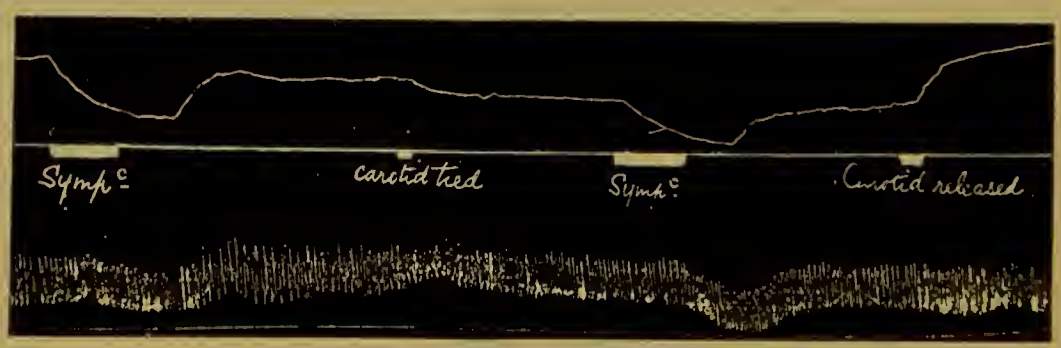

Fig. 21. Dog. Effect of sympathetic stimulation before and after ligature of carotid on same side. The opposite carotid had been ligatured previously. After the second excitation the gland-volume did not return to normal until the blood-flow through the carotid had been re-established.

Stimulation of the divided sympathetic produces at first a distinct effect on the volume of the gland after ligature of both carotids. In Fig. 21 it will be noticed that the gland did not return to its original volume after stimulation of the sympathetic until the blood-flow through the carotid had been restored.

Effect on the volume of the submaxillary gland of successive stimulation of the chorda and sympathetic nerves.

Inasmuch as stimulation both of the chorda and of the sympathetic tends normally to bring about diminution of the total volume of the gland, no great difference might be expected to result according to which nerve is first stimulated and which subsequently. The effect of the second excitation is, however, greater if the chorda be first stimulated, more especially if this stimulation be repeated several times, and the sympathetic then stimulated immediately afterwards. This is no doubt due, firstly, to the augmented secretion which the previous chorda excitation has induced, and, secondly, to the vaso-constriction of the gland which the sympathetic stimulation produces.

When the sympathetic is first stimulated, and then immediately afterwards the chorda, not only may there be no additional fall of the lever as a result of the second stimulation, but the fall caused by the sympathetic excitation may be even succeeded by a rise.

When a dose of atropine has been given sufficient only to paralyse the secretory fibres of the chorda, simultaneous stimulation of both chorda and sympathetic with the same strength of current causes first diminution, succeeded later by increase of the gland-volume (Fig. 22). By diminishing the strength of the sympathetic stimulation while the strength of the current applied to the chorda remains unaltered, a point may be reached where simultaneous stimulation of the two nerves produces no alteration of the gland-volume. Stimulation of the sympathetic while the gland is dilated from chorda excitation always produces diminution of the dilatation, and if the current is sufficiently strong, diminution of the gland-volume to a point below that at which it stood before the chorda was stimulated.

In view of the theory put forward by Mathews[1], that sympathetic secretion in the submaxillary gland is brought about by muscular mechanism, I have, at Professor Langley's suggestion, carried out some experiments in order to determine what is the effect on the gland-

[1] *Ann. N. Y. Acad. Sci.* xi. no. 14, 1898.

volume of sympathetic stimulation with the duct clamped under conditions where the sympathetic produces a free flow of watery

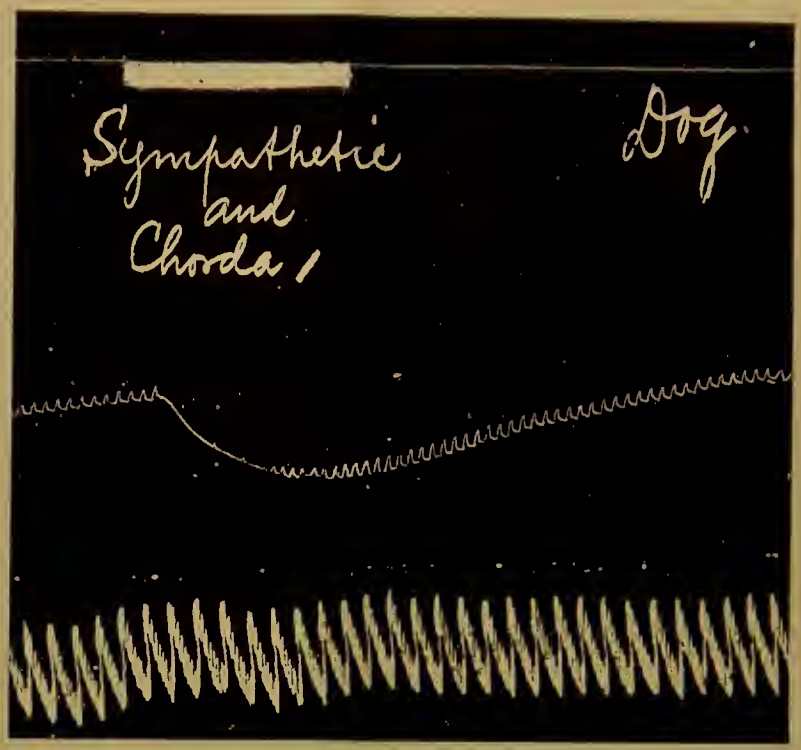

Fig. 22. Dog. Simultaneous stimulation of chorda and sympathetic nerves after administration of a small dose of atropine. The sympathetic stimulation was slightly stronger than that of the chorda, and the after-dilatation due to stimulation of the fibres of the latter was not seen.

secretion. In one experiment, a dog weighing 8·2 kilos. was kept under the influence of A.C.E. mixture, and the right submaxillary gland (volume 6·9 c.c.) was placed in the plethysmograph after being freed from its capsule, but without any veins tied. The chorda and sympathetic nerves were both placed upon Ludwig's electrodes, connected with a reverser. The right chorda was stimulated intermittently with the coil at 12 cm. for 12 minutes, each stimulation causing diminution of the volume of the gland and a free flow of secretion from the duct. When the secretion caused by the last stimulation had ceased, the duct was clamped, and the sympathetic stimulated. The first effect was to produce a distinct dilatation of the gland, which was followed by a shrinking due to the vaso-constrictor action of the nerve, the general blood-pressure, however, remaining constant (Fig. 23).

A second stimulation of the sympathetic with the duct again clamped after the gland-volume had returned to normal showed only shrinking of the gland. The chorda was then stimulated intermittently

for 10 minutes and the same experiment repeated. A primary dilatation of the gland was succeeded by diminution of its volume as the vaso-constrictor effect ensued, and this result was obtained in two more experiments when preliminary chorda stimulation gave rise to well-

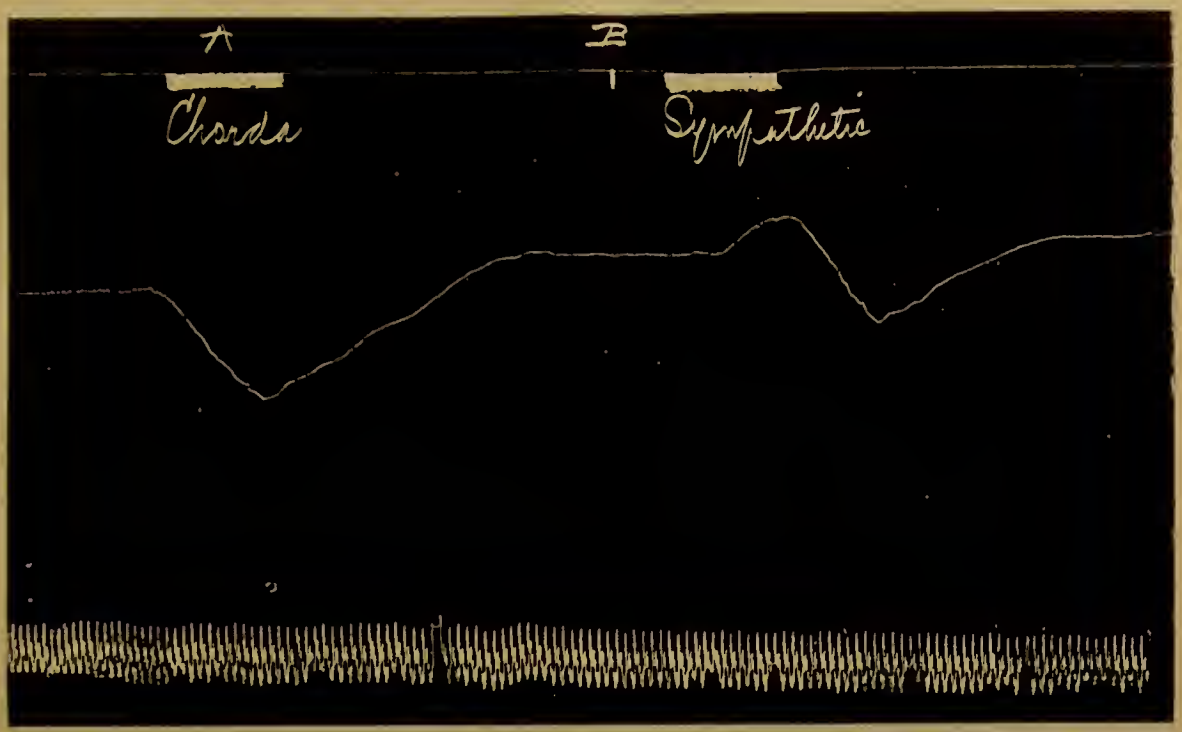

Fig. 23. Dog. The chorda was stimulated intermittently for 12 mins., the last stimulation being recorded at *A*. The gland-duct was clamped at *B*, and the sympathetic then stimulated. The first effect of the stimulation was an increase in volume of the gland.

marked augmented secretion. This increase of volume could not have been due to any dilatation of vessels of the gland, nor could it be caused by contraction of muscular or other contractile substance within or about the gland, it must therefore be due to the influx of fluid into the gland, from the blood vessels through the lymph spaces. The evidence brought forward by Mathews in favour of the muscular mechanism of sympathetic secretion does not appear to be altogether conclusive, but one of the greatest difficulties that this theory has to contend with is that of demonstrating the presence of any contractile substance which can act as he suggests. That the gland-capsule has nothing to do with sympathetic secretion is easily demonstrated, squeezing out of secretion by constriction of the meshwork of blood vessels is unlikely in view of the facts of chorda secretion, and the existence even of scattered muscular fibres around or between the alveoli is problematical. That there are muscular fibres in the walls of the ducts is of course true, and

it seems reasonable to assume that they might contract on nerve stimulation, whether of sympathetic or chorda, but this is scant reason for asserting that the secretory action of the sympathetic is brought about by means of a muscular mechanism. The argument that the flow of saliva is greatest when the sympathetic is first stimulated, that it gradually diminishes and then stops, and that it must therefore be forced out by muscular contraction appears to me to be quite invalid, nor does the return of secretion on sympathetic excitation after fluid has been injected into the ducts prove the point. In experiments which I have myself made, the augmented secretion obtainable on sympathetic stimulation after the chorda has been excited diminished very considerably in amount after the first ten seconds, but the gland still secreted a certain amount of saliva during the continuance of stimulation for several minutes. If after sympathetic stimulation had ceased to produce an appreciable amount of secretion a solution of normal saline was allowed to pass into the duct under pressure of a height of 1 cm. of fluid, only $\frac{1}{100}$ to $\frac{1}{50}$ c.c. of saline solution entered the duct. Stimulation of the sympathetic with the same strength of stimulus as before then gave rise to an amount of secretion varying from ·01 to ·015 c.c. as against ·002 c.c. in ten seconds before the injection. The quantity of secretion amounted therefore to five times the amount obtained before the injection of saline solution into the duct, but, in view of the very small quantity of fluid so injected, I see no reason why it should have passed into the alveoli of the gland, or indeed farther than the duct itself, and have simply been forced out of the duct again on sympathetic stimulation by contraction of the muscular fibres of the duct wall. These experiments were on dogs, but in the cat Mathews appears to have been able to force back as much as $\frac{1}{10}$ c.c. of fluid into the duct by blowing. Even if experiments performed under such necessarily abnormal conditions have to be taken into account, it seems quite possible that the gland cells can take up fluid from one side of the cell as well as from the other, and again secrete it when the sympathetic is stimulated without the intervention of any muscular mechanism.

Stimulation of afferent nerves.

It has been shown by Lovèn, Grützner and Heidenhain that stimulation of the central end of sensory nerves causes rise of general blood-pressure, and this rise of pressure is accompanied in curarised dogs by some amount of secretion and diminution in volume of the submaxillary gland. Fig. 24 shows the gradual fall of the plethysmo-

graphic lever on stimulation of the central end of the sciatic nerve in a dog. After administration of a large dose of curare this effect was no longer obtained.

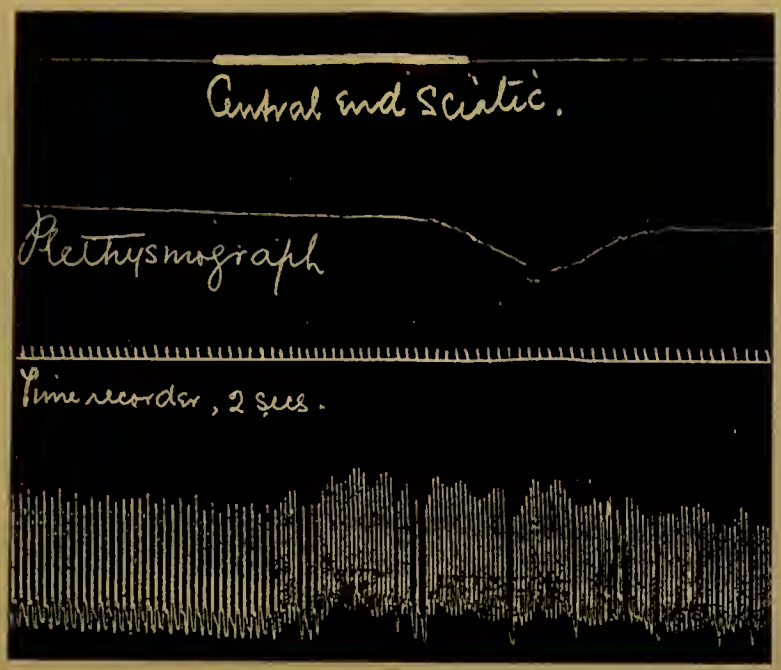

Fig. 24. Dog. Effect on volume of gland and on blood-pressure of stimulation of central end of divided sciatic nerve.

In view of the statement that the flow of saliva when the submaxillary is secreting can be inhibited by stimulation of the central end of an afferent nerve, I have attempted to determine what effect such stimulation has upon the diminished volume of the gland, in which secretion has been induced either by pilocarpine or chorda excitation. The anæsthetic was varied in different ways in order to eliminate any possible error arising from such a cause. I was, however, unsuccessful in producing any diminution of the constriction of the gland, or any return of the volume of the gland towards the normal by stimulation of the central end of a sensory nerve, although the excitation produced a diminution in the flow of saliva. In most cases, indeed, the volume of the gland underwent still further diminution as a result of the stimulation, and seeing that the flow of saliva was inhibited this result must have been due to constriction of the vessels of the gland.

Summary.

From the results given in this paper it is evident that the changes in volume of the submaxillary gland as recorded plethysmographically can be divided into two classes—passive and active.

As we should expect, the gland reacts passively to changes in the general blood-pressure, its volume rising and falling synchronously with the latter. Thus we get a shrinkage of the gland on stimulating the peripheral end of the vagus or on clamping both carotids, either of which procedures diminishes the supply of blood to the gland. On the other hand the gland swells synchronously with the rise of blood-pressure which normally follows the cessation of vagal inhibition. The active changes in volume of the gland are conditioned by two factors, vascular and secretory. In many cases both these factors are involved, the result being an algebraic summation of the effects of each factor.

In order to study the pure vascular effects, our observations must be made on a gland which has been poisoned with atropine. In such a case the vaso-dilatation brought about by chorda stimulation causes a swelling, whereas we get a shrinking of the gland on stimulation of the central end of a sensory nerve, evidently in consequence of a reflex vaso-constriction. Stimulation of the peripheral end of the sympathetic also causes diminution of gland-volume in consequence of vaso-constriction, but it is difficult in this case to eliminate the coincident effects of the secretory fibres of the sympathetic, since these latter are not affected by ordinary doses of atropine.

All activity of the gland accompanied by secretion causes a diminution in its volume, a diminution so marked that in most cases it overpowers the effects of any simultaneous vaso-dilatation, so that, *e.g.* stimulation of the chorda in the unpoisoned animal causes a marked shrinking. By allowing for the swelling of the gland which would be produced by the dilatation, we can determine the actual diminution in volume of the extra-vascular elements of the gland. On comparing this with the amount of secretion poured out in the same time, we find that at least nine-tenths of the secretion are derived from the extra-vascular portions. Since there is no diminution in the lymph-flow from the gland, but rather a slight increase during the period of stimulation (Bainbridge), we must conclude that the effect of the secretory nerves is simply and solely upon the secretory cells, the increased exudation from the blood vessels which must in the last instance supply the fluid for the secretion being a secondary phenomenon determined entirely by the metabolic changes of the cells and lagging behind these to a very considerable extent. I have been unable to confirm in any way the view put forward by Mathews that the sympathetic secretion is due to a contraction of unstriated muscular fibres in the gland.

Conclusions.

1. Changes in volume of the submaxillary gland may be brought about both by variations in the flow of blood to the gland and of secretion from the gland.

2. Nicotine and coniine when injected intravenously bring about a diminution of the gland-volume by constriction of the gland vessels and by causing a flow of secretion from the gland.

3. No difference in this action of nicotine can be observed after division of the chorda tympani and excision of the superior cervical ganglion.

4. Intravenous injections of pilocarpine cause diminution in volume of the submaxillary gland accompanied by a free flow of secretion.

5. Injections of a saline decoction of one submaxillary gland of a dog cause a preliminary diminution followed by a slight increase in volume of the remaining submaxillary gland, but no appreciable effect on secretion.

6. Cardiac inhibition, whether produced by vagus stimulation or by drugs, is followed by shrinkage of the gland. When this shrinkage is brought about by vagus stimulation it is followed after the stimulus has been removed by an after-dilatation.

7. Stimulation of the chorda tympani nerve causes diminution in volume of the submaxillary gland, followed by after-dilatation.

8. After the administration of a dose of atropine sufficient to paralyse the secretory fibres of the chorda, excitation of the chorda causes dilatation of the submaxillary gland.

9. The fluid poured out as a result of stimulation of the secretory fibres of the chorda is derived from the secretory cells of the gland, and only secondarily from the blood vessels.

10. Sympathetic stimulation causes shrinkage of the gland, and a maximum effect is obtained when the chorda has been subjected to repeated previous excitation.

11. Continuous stimulation of the chorda after blockage of the gland-duct causes maximum dilatation of the gland.

12. The diminution in gland-volume produced as a result of chorda stimulation can be still obtained for some minutes after both carotids have been tied.

13. Stimulation of the central end of a sensory nerve produces diminution in volume of the submaxillary gland.

14. There is no evidence to show that sympathetic secretion is brought about through the medium of a muscular mechanism.